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TITLE: Modulating Calcium Signals to Boost AON Exon Skipping for DMD

PRINCIPAL INVESTIGATOR: M. Carrie Miceli

CONTRACTING ORGANIZATION:

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PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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Modulating Calcium Signals to Boost AON Exon Skipping for DMD

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5b. GRANT NUMBER
W81XWH-15-1-0182

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

M. Carrie Miceli

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

UNIVERSITY OF CALIFORNIA, LOS ANGELES
10889 Wilshire Blvd., Suite 600
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8. PERFORMING ORGANIZATION REPORT NUMBER

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U.S. Army Medical Research and Materiel Command
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13. SUPPLEMENTARY NOTES

14. ABSTRACT

AON-mediated exon skipping is currently advancing as therapy for DMD, though levels of dystrophin produced remains suboptimal. Thus, identification of compounds with the capacity to boost exon skipping could help fully realize this potentially life-changing DMD treatment. We have assessed whether dantrolene, an already FDA-approved drug, can boost efficacy of AON exon skipping in the context of AON targeting skipping of exons 51, 44 or 45. Additionally, we have begun testing proprietary compounds that regulate the same Ca2+ pathway regulated by dantrolene for skip-boosting. . As a second objective we are assessing these compounds for their ability promote exon skipping in patient cells with DMD mutations that have a low level endogenous skipping, dystrophin expression and/or mild phenotypes. Preliminary data indicate that these compounds are effective in at least a subset of patient cell models; one candidate may boost skipping even better than dantrolene. Based on its known activity, this compound promises greater efficacy and a wider therapeutic window than dantrolene. Planned studies will combine chemical genomics with RNA Seq analysis to identify mechanisms of activity and specificity in order to guide discovery of second-generation skipping drugs or combinations with greater activity.

15. SUBJECT TERMS

Exon skipping, Dantrolene, Calcium, Duchenne, Dytrophy, Dystrophin, anti-sense-oligonucleatide, DMD, RNA therapeutics.

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	15	19b. TELEPHONE NUMBER *(include area code)*

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1. INTRODUCTION

AON-AON-mediated exon skipping is currently advancing as therapy for DMD, though levels of dystrophin produced remain suboptimal. Thus, identification of compounds with the capacity to boost AON-directed exon skipping may help fully realize this potentially life-changing treatment for DMD. Here, we will assess whether dantrolene, an FDA-approved drug already demonstrated to boost efficacy of AON exon skipping in the context of e45-50 DMD deletions, is also relevant to other mutations amenable to exon 51 skipping or to other exon 44, 45 or 53 AON/DMD mutation skip combinations currently in the clinical trial pipeline.
Additionally, we will test the two proprietary compounds that regulate the same Ca2+ pathway regulated by dantrolene for their activity in boosting AON-directed exon 51, 44, 45, or 53 skipping. Based on their known activity, these compounds promise greater efficacy and a wider therapeutic window than dantrolene. As a second objective we will assess the ability of these compounds to promote exon skipping in patient cells with *DMD* mutations that have a propensity for low level endogenous skipping, dystrophin expression and/or mild phenotypes. We hypothesize that these compounds may promote skipping in the absence of AON, and thus would represent a cost effective alternative to AON skipping for a subset of very rare mutations. Finally, we hypothesize that by combining chemical genomics with RNA Seq analysis we can begin to identify mechanisms of compound activity and specificity in order to guide second-generation drug discovery.

2. KEYWORDS

Exon skipping, dantrolene, Calcium, Duchenne, Dystrophy, dystrophin, anti-sense-oligonucleatide, DMD

3. ACCOMPLISHMENTS

What were the major goals of the project?

Specific Aim 1:
Major Task 1 – Testing RyR pathway antags on DMD patient cells with e51, e45, e44 and e53 skippable mutations

Subtask 1 - Develop skipping conditions and readouts for skipping exons 44, 45 and 53 in patient derived cells (6 months; 90% complete).

This task has been largely completed for exons 44 and 45 and are described in Figures 1 and 2. We have begun to assess exon 53 skip conditions, but have yet to utilize them routinely. Because we have exon 44 skip and exon 45 skip DMD culture models routinely and efficiently growing and differentiating, we have chosen to focus on these cell models first. To date it appears that RyCal pathway skip boosters can function across every mutation type we have tested; mouse exon 23, human exon50 reporter, human exons 51, 45 and 44. Further, given that dantrolene can boost both PMO and 2 omethyl AON it may also be agnostic to AON backbone.

Subtask 2 - Test compounds on 51, 44, 45 and 53 skippable cells for activity in combination with AON. Search for sequence motifs in intron/exons that correlate with compound activity (6-36 months; 85% complete).

We have previously demonstrated that RyR antags can boost AON directed exon 51 skipping in patient derived iDRM.

To assess conditions for boost activity on skipping DMD mutations rendered in frame by exon 45 skipping, we performed a dose escalation (125, 250, 500 or 1000nM of E45AO) with or without Dantrolene 50nM to determine best boosted AON concentration. 500nM AON was used in subsequent assays with or without drugs at indicated concentrations. Fig 1 demonstrates that all three RyRantags boost AON H45A (AON) (Wilton et al 2007) exon 45 skipping in DRMCDMD1003 (delta 46-51) in a dose dependant way. This is exciting as it identifies additional poteintial drugs for development as skip boosters. Figure 2 demonstrates that AON mediated exon 44 skipping is also boosted by RyRCal2 in patient CDMD1015iDRM. While boost is modest,

we anticipate a greater boost with lower AON concentrations. Additional iDRM testing and dosing is under way to determine weather all exon 45, 44 or 51 skips can be boosted. We have found that a second exon 45 skippable cell model, cDMD iDRMCD451006 is boosted similarly. We have yet to begin assessing activity on 53 skippable cells.

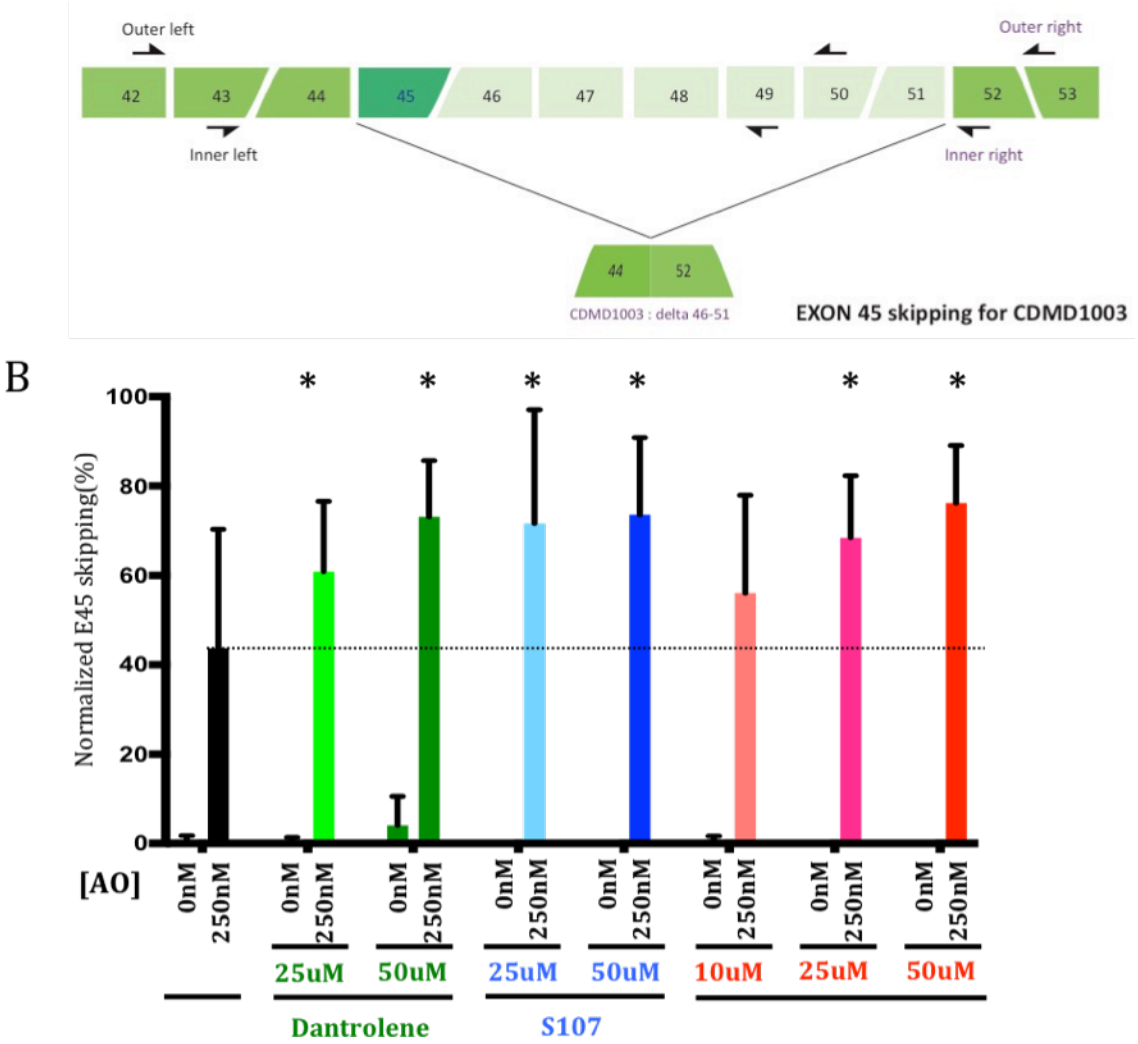

Figure 1. RyRantags boost exon 45 skippping in patient cell CDMD1003iDRM. iDRMs (inducible directly reprogrammable myotubes) were reprogrammed to myotubes in culture and treated with indicated concentrations dantrolene (green), S107 RyCal (blue) or the proprietary RyRantag (red) in the presence of absence of exon 45 skipping AON and the degree of skipped and unskipped RNA quantitated. Normalized E45 was calculated as the ratio of skipped/unskipped+skipped. For these experiments iDRM were seeded at 200,000 cells per well in fibroblast growth media (DMEM (+phenol red, high glucose) + 15% Fetal Bovine Serum (FBS) + 1% Nonessential amino acids + 1% pen/strep) in 6-well plates (Corning) pre-coated for 1 hour with 0.1% gelatin (sigma). The following day, 5µM 4OH-tamoxifen (Sigma; resuspended in ethanol) was added in fibroblast growth media for 24 hours. On day 3, cells were washed in 1 x Phosphate Buffered Saline (PBS; Invitrogen), and fusion media containing 1µM 4OH-tamoxifen was added (1:1 Ham's F-10:DMEM (phenol red free, high glucose), 2% Horse Serum, 2% Insulin-Transferrin-Selenium). On Day 4, cells were transfected with 2-O-methyl AO (MWG Operon) using oligofectamine (life technologies) according to the manufacturer protocol. AO was removed on the following day, cells were washed with 1XPBS, and fresh fusion media containing 1µM 4OH-tamoxifen was added with titrating concentrations of drug and carrier controls. Forty-eight hours later, cell pellets were harvested and frozen for subsequent RNA isolation and exon skipping analysis via nested PCR with primers encompassing the deleted region.

. *P<0.05 P values reflect a Students t test. Bars represent means of triplicate determinations.

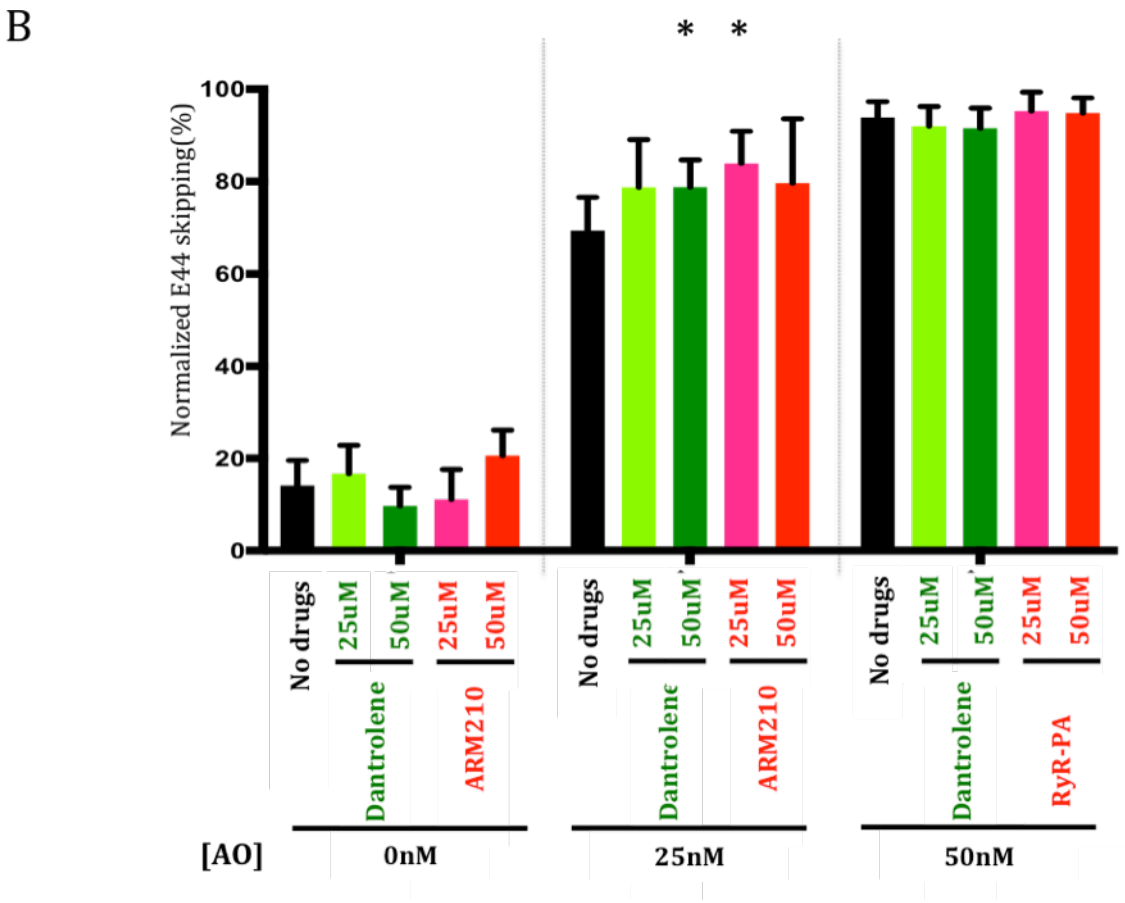

Figure 2. RyRantags boost exon 44 skipping in patient cell CDMD1015iDRM (delta 45). iDRMs (inducible directly reprogrammable myotubes) were reprogrammed to myotubes in culture and treated with 0, 25, or 50nM AON alone or in combination indicated concentrations of dantrolene , S107 RyCal or a proprietary RyRantag (RyR-PA). The degree of skipped and unskipped RNA quantitated. Normalized E44 was calculated as the ratio of skipped/unskipped+skipped. The antisense oligonucleotide H44A (Wilton et al 2007) in the CDMD1015 (delta 45) cell line. *P<0.05 P values reflect a Students t test. Bars represent means of triplicate determinations.

Milestones Achieved

Prioritize 2 iDRM most sensitive to RyR antags for RNASeQ (18 months; 100% complete)

We have prioritized 2 iDRM based on our findings. CDMD1003, is among the most sensitive to exon 45 AON/RyRantag boost. We have additionally prioritized CDMD1015, shown to have endogenous exon 44 skip activity and to be sensitive to e44AON/dantrolene boost.

Determine relative efficacies of Dantrolene and other calcium modulators for synergizing with AON to promote e51, e44, e45, and e53 skipping (36 months; 75%). We have demonstrated that, like Dantrolene, one of the proprietary RyRantags tested can boost exon skipping. We have demonstrated this in e44, 45 and partially in e51 skippable iDRM. To determine the relative efficiencies RyRantags additional side by side dose responses on multiple cells are underway. Once we have finished our studies in e51,e44 and e45 before we move onto exon 53.

HRPO/ACURO Approval

Specific Aim 2
Major Task 1 - Testing RyR pathway antags for activity on DMD patient with suspected propensity to

skip.

Subtask 1 - Test compounds on 44 skippable cells for activity in absence of AON (6-36 months; 70% complete).

We have tested patient derived cells with mutations amenable exon 44 skipping to correct reading frame. It has been suggested that boys with these mutations have a milder disease course due to an increased propensity to constitutively skip exon 44 to produce low levels of dystrophin.

We find that some patient derived exon 44 skippable reprogrammed lines demonstrate increased levels of endogenous exon 44 skipping to restore reading frame (Fig 3**).** Further, preliminary findings indicate that RyR antags can boost this endogenous exon 44 skipping in the absence of AON in some patient cells (not shown). We continue to screen exon 44 skippable iDRM to determine whether dantrolene can boost levels of natural exon 44 skipping. We are on target for completion within 36 months.

Subtask 2 - Develop skipping conditions and readouts for skipping exons 44 , 45 and 53 in patient derived cells (6-18 months 90% complete).

Conditions and readouts have been developed for exons 44 and 45, but not fully for 53 yet.

Subtask 3 - Test compounds on exon 30, 31, 32 skippable lines (18-32 months, 60% complete).

These lines are derived from patients with a mild phenotype and/or other reasons to suspect endogenous skipping. We find that the exon 30 and 32 skippable line tested do exhibit high levels of endogenous skipping, as hypothesized, and some demonstrate increased skipping in the context of RyR antags even without AON. We are in the process of assessing whether dantrolene can boost natural skipping in these lines. Should dantrolene boosts natural skipping in these lines will be significant because dantrolene is already FDA approved and can be used in the absence of AON in these rare mutations unlikely to have effective skipping AON developed in the next few years. Further, dantrolene is much less expensive and more readily available than skipping AON.

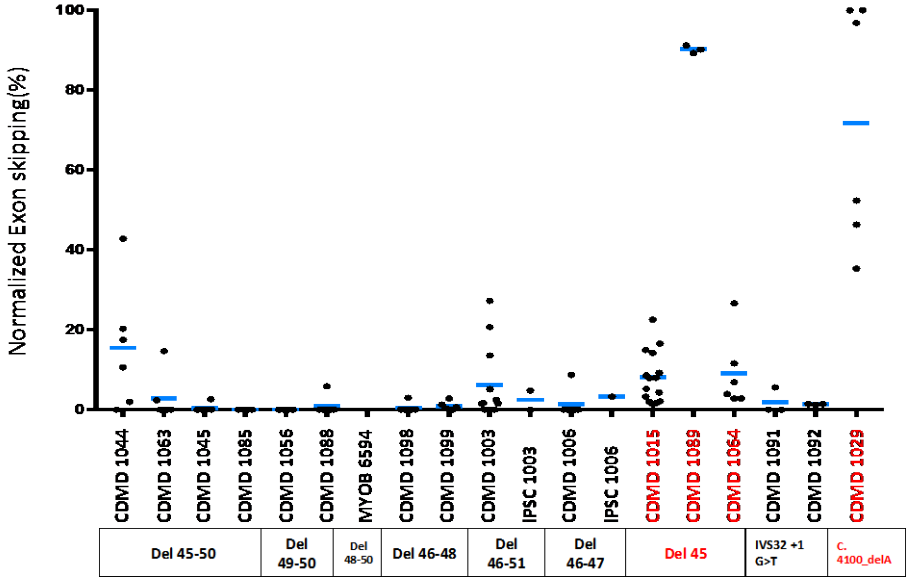

Fig 3. Some iDRM from patients identified as mild phenotypes show a propensity to skip. Levels of endogenous/natural skip message were identified for 45, 44 and 51 skips as in Figures 1 and 2. Primers were identified for described in Figs 1 and 2. Specific primers were developed for detection of exons 30 and 31 and 32 skips.

Milestone Achieved:

Identify iDRM with mutations amenable to skipping by RyR antag alone (month 36, 60% complete).

We have identified several iDRM with some degree of autoskip (Fig. 3). We hypothesize that RyRantags may boost endogenous skipping further in response to RyR antags alone. Initial studies indicate some boost in at least some of the lines identified. Additional testing will allow us to repeat, validate and extend our preliminary findings.

Specific Aim 3

Major Task 1 - Using chemical genomics and RNA seek to identify skip regulatory pathways and targetable effectors

Subtask 1 - Probe RyR/Ca2+ pathway components with known inhibitors or readouts to establish relationships between effectors and skipping activity (6 months).

Preliminary findings indicate that CAM kinase inhibitors boost skipping, both alone and in addition to dantrolene. Ongoing experiments will titrate inhibitors and dantrolene alone and in combination to determine if the are completely redundant since they both target the same calcium regulated pathway or, rather, if their effects are truly additive because CAM kinase targets a pathway(s) in addition to those regulated by RyR to boost skipping further. Toxicity with high doses of inhibitors has presented as a problem in these studies, limiting our ability to fully complete.

Milestone Achieved: Identification of candidate regulatory pathway skipping (6 months).

This milestone was not reached due to unanticipated drug toxicity.

Major Task 2 - Use RNA Seq, pathway and regulatory sequence analysis

Subtask 1 - Optimize alternate splicing assay using exon capture and RNASeq (12 months, 80% complete). We have begun optimizing the exon capture and performed preliminary RNASeq experiments as described using exon capture.

Subtask 2 - High depth RNASeQ on compound treated versus untreated iDRM (deep analysis in repeat experiments with 2 different iDRM most sensitive to RyR pathway antag boost; 18 months, 70% complete).

We have performed high depth sequencing on one pair of treated versus untreated exon 51skippable CDMD5017iDRM. Subsequently we have found CDMD1003 (exon 45 skippable) and CDMD 1015 exon 44 skippable culture model as the two most sensitive to RyR pathway antagonists as boosters. As shown above in Figure 2, we find CDMD1015 iDRM expresses low levels of natural skipping and can be induced to skip even more with AON targeting Exon 44 exclusion and RyRpathway boosters. We are in the process of collecting RNA from treated and untreated differentiated cell CDMD1015 cultures and anticipate RNASeQ experimental results and preliminary data early next year. We have some concern that the first experiment with 5017 was contaminated with fibroblast due to incomplete differentiation. If CDMD1015 analysis is worthwhile and we determine that 5017 is not as well differentiated, we may perform RNASeQ on CDMD1003. In addition to enabling novel discovery regarding RyCal pathway boosters mechanism(s) of action, these experiments will give a much more accurate quantitation of skipped and unskipped mRNA, if more than one exon is being skipped, and if there are any off target effects. In light of recent FDA approvals for exon skipping drugs, issues of accurate quantiation of DMD skipping are becoming even more important.

Subtask 3 - Exon-intron motif and transcriptional pathway analysis based on RNASeQ and candidate regulatory motifs identified in Aims 1 and 2 (12-24 months; 0% complete).

We have yet to initiate these studies. One concern raised from our first RNA SeQ analaysis is likely incomplete differentiation leading to inclusion of fibroblast RNA. However, since then we have better optimized our differentiation procedure. Therefore we will wait for this RNASeQ analysis to be complete for initiation of transcription pathway analysis. The results will be compared with those from the first performed the RNASeQ analysis. Once analysis of initial treated and untreated iDRM pair is complete we will be able to initiate these studies. We are on track to complete these experiments by the end of the granting period.

Subtask 4 - Test candidate pathway effector activity patient derived cell(s) (24-36 months).

Based on our chemical genomics RyR pathway discovery findings, we have begun testing CAM kinase inhibitors for boost skipping activity. Preliminary evidence indicate that they, too, have skip-altering activity, implicating CAM kinase signaling in RyR mediated skip boosting, and aiding in identification of downstream signaling and modulation of RNA splicing. Identifcation of CAM kinase involvement provides an additional target for skip boosting.

What opportunities for training and professional development has the project provided?

These studies have served as a professional development opportunity for trainees Derek Wang, PhD candidate who just defended his Ph.D in October and postdoctoral fellow, Florian Barthelemy, PhD. Most recently, I have recruited an Assistant Research Professor with experience in cell differentiation models to join our group focused on patient derived cell models, working together with Dr. Barthelemy. Dr. Barthelemy has presented his initial findings at highly relevant meetings listed below. Florian has mentored undergraduate students, gaining experience as a teacher and supervisor. Both trainees participated in the CDMD student and post-doctoral training program, which includes presenting and participating in biweekly CDMD inter-group meetings, an annual retreat, and hosting and attending seminars. While not a stated objective of this grant, trainee career development is a major focus of the CDMD.

Oral presentation at the AMC – (San diego, September 22nd 2017)
F. Barthelemy, R,T Wang, Christopher Hsu, E. Douine, A. Pyle, S, F. Nelson, M.C. Miceli
RyR pathway antagonists for combination therapy to boost exon skipping in human DMD patient derived culture models
Posters presenteation at the Moving Target 2017 – Precision Medicine (Los Angeles, August 17th 2017)
F. Barthelemy, R,T Wang, Christopher Hsu, E. Douine, A. Pyle, S, F. Nelson, M.C. Miceli
"Identification and evaluation of drugs targeting the RyR pathway for combination therapy to boost exon skipping in human DMD patient derived culture models"

How were the results disseminated to communities of interest?

Dr. Florian Barthelemy presentations listed above.

What do you plan to do during the next reporting period to accomplish the goals?

Over the next year we hope to have identified an exon 53 skippable cells that robustly grows and differentiates in culture. If we do not, our focus will remain on exons 51, 44 and 45. We anticipate writing 1 or 2 manuscripts from our findings in the next reporting period: 1) developing and using our well developed exon 45 and exon 44 skipping patient models to demonstrate that dantrolene can also boost exon 45 and 44 AON. We will soon know the degree to which RyCal pathway antagonists can boost endogenous skipping in the patient models described above. These results will be included in this manuscript, if they are sufficiently robust. 2) The

identification of a novel RyCal with capacity to boost exons 45 and 44 will likely warrant its own second manuscript. There is some possibility the manuscripts will be combined reporting an analysis of dantrolene and RyCal pathway inhibitors and expanded target exons in the same manuscript.

4. IMPACT

What was the impact on the development of the principal discipline(s) of the project?

Short term: The research completed has identified boosters of AON-mediated exon skipping in the context of specific patient iDRM . By testing RyR antags in combination with AONs targeting exons 51, 45, and 44 on a panel of patient-derived myotubes with common *DMD* mutations, these studies inform on DMD patient populations that might benefit from combination AON/RyR-antag therapy. ExonDys51, and AON targeting exon 51 skipping, is now commercially available by prescription for qualifying patients and second generation exon 51 drugs are already in the trial pipeline. Sarepta is currently now performing a phase 3 trial for their exon 45/53 skipping cohort. Thus our findings are expected to inform on mutations most appropriate to move into clinical trials in combination with AON. Therefore, there is potential for planning a clinical trial combining exon 45 or 51 AON with dantrolene. In addition, the mechanistic studies may highlight novel and potentially more effective means by which to boost exon skipping and second generation agents that can be tested to broaden the impact of exon skipping in DMD.

Long term Impact. We anticipate that there will be substantial long-term gains from the early and proposed research. Exon skipping is a now emerging therapy designed to correct the proximate genetic cause of DMD by inducing the expression of internally truncated protein associated with the much milder BMD. Once optimized it is predicted to significantly benefit up to 80% and enhance quality of life through slowing of disease progression. This will likely extend life directly. However, variation in patient response, suboptimal induction of dystrophin protein and clinical response clearly indicate that additional work is warranted to enhance the therapeutic potential of exon skipping. The work performed supports potential utility of dantrolene and other RyCals as adjuvant to exon skipping when used together with AON to boost exon skipping efficacy. The work assessing using RyRantags to boost endogenous skippers may enable its use alone therapeutically in a subpopulation of Duchenne patients with particular mutations. This will particularly impactful for rare mutations for which the development of AON is not yet in the development pipeline.

Together with our recent demonstrating safety and efficacy of dantrolene in the mdx DMD model after long-term (6 month) oral dosing (funded outside this grant), our findings here findings provide preclinical evidence in support of planning a clinical trial wherein dantrolene is combined with either exon 51, 45 or 44 skipping drugs. Because Exondys51 and dantrolene are both already FDA approved, we are now writing clinical trial planning grant proposal aimed at developing ExonDys51/dantrolene combination. Should the need for skip boosters persist, we may move forward testing other RyCal inhibitor and exon skipping drug combinations.

What was the impact on other disciplines?

With the initial successes of AON mediated exon skipping in DMD, RNA splice modulation technology is being applied to several rare diseases, i.e. SMA, myotonic dystrophy and others. Compounds demonstrated to boost DMD exon skipping alone or in the context of AON in DMD represent prime candidates to asses for splice altering activity in other disease setting.

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

Our findings promise to provide the public knowledge regarding exon skipping and RNA therapeutics.

5. CHANGES/PROBLEMS

Nothing to Report

6. PRODUCTS

Publications, conference papers, and presentations

Poster Presentatio at the New Directions in Muscle Cell biology meeting, 2016; Dr. Florian Bartolomy .
Oral presentation at the AMC – (San diego, September 22nd 2017)
F. Barthelemy, R,T Wang, Christopher Hsu, E. Douine, A. Pyle, S, F. Nelson, M.C. Miceli
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7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: M. Carrie Miceli
Project Role: PI
Researcher Identifier (e.g., ORCID ID): NA
Nearest person month worked: 2 cal mos
Contribution to Project: PI Dr. Miceli oversees all experiments helps with data interpretation and data publication.

Name: Stanley Nelson
Project Role: Co-I
Researcher Identifier (e.g., ORCID ID): NA
Nearest person month worked: 1 cal mos
Contribution to Project: Dr Nelson is an expert in RNAseq and DMD genotype phenotype correlations. He advises us on aims 1-2 and is key to the execution of Aim3.

Name Florian Barthelemy
Project Role: Post Doctoral Fellow
Nearest person month worked: 9 cal mos
Contribution to Project: Florian Barthelemy: (post-doctoral fellow, Miceli lab) has taken the lead on developing all of the skipping reagents and performing assays assessing Rycal skip activity in a number of patient derived cells.

Name: Derek Wang
Project Role: Graduate Research Student
Nearest person month worked: 2 cal mos
Contribution to Project: Mr. Wang has assisted Dr. Barthelemy on assay development, ddPCR studies, patient cell banking reprogramming and differentiation.

Name: Ekaterina Mokhonova
Project Role: Staff Research Assistant
Nearest person month worked: 3 cal mos
Contribution to Project: Ms. Mokhonova has been involved in banking cells and assessing pathway inhibitors in patient derived cells.

Name: Deirdre Scripture-Adams
Project Role: Staff Research Assistant
Nearest person month worked: 5 cal mos
Contribution to Project: Dr. Scripture Adams has significant experience with human stem cells, directed differentiation, development of complex organ culture models for cell fating. For the past months, she has been involved in expansion, differentiation and purity assessment of reprogrammed DMD patient fibroblasts. Her expertise has helped in achieving reproducibility of differentiated cultures, which had proven to be a challenge. She will continue to develop most robust muscle lineage differentiation in culture from reprogrammed fibroblasts to enable greatest reproducibility and fidelity.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

See Other Support page

What other organizations were involved as partners?

Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

Nothing to Report

9. APPENDICES

Nothing to Report

OTHER SUPPORT

MICELI, M. CARRIE, Ph.D.

PREVIOUSLY ACTIVE GRANT HAS CLOSED

CIRM TRX-05426 3/1/2013- 2/28/2015 3.6 cal months
PI: Stanley Nelson; Co-PI: M. Carrie Miceli
Title: Combination Therapy to Enhance AntiSense Mediated Exon Skipping for Duchene Muscular Dystrophy
Major Goals: To perform all preclinical assessment, dose ranging and efficacy and toxicology studies required to enable IND application and 100% clinical trial readiness for a combined therapeutic CDMD51Plus for use in exon skipping for DMD. Dr. Miceli will oversee all UCLA preclinical studies.

Penn/UCLA Wellstone Center Grant 7/01/10-6/30/15 0.6 cal months
PI: Lee Sweeney, University of Pennsylvania
Co-PIs/collaborators:Drs. McNally, Univ. of Chicago; Walter and Vandenborn; University of Florida; Spencer, Miceli, Nelson, UCLA and Ostap and Finkel, Penn
Title: Failed Regeneration in the Muscular Dystrophies: Inflammation, Fibrosis and Fat
Major Goals: As a collaborator with Dr. Spencer (subcontract PI), we examine the immune response to anti-fibrotic therapies.

UCLA Broad Stem Cell Research Center 8/25/14-8/24/15 1.2 cal months
Innovator Award
PI: M. Carrie Miceli
Major Goals: This award is to recognize and enable pursuit of Stem Cell Approaches to Combination Exon Skipping.

ACTIVE

P30 AR057230-06 4/1/14-3/31/19 1.2 cal months NIH/ NIAMS
PI: M. Spencer; Co-PI: M. C. Miceli
UCLA Muscular Dystrophy Core Center
(Miceli: Director of the High Throughput Screening and Cell Repository Core B and Member of the Executive Committee Core A). The goal of this grant is to establish a Muscular Dystrophy Center on the UCLA campus, consisting of research cores, pilot and feasibility funding and an administrative core that will facilitate translational research in the area of muscular dystrophy.

University of Florida, 8/01/15-7/30/20 0.6 cal months
PI: Lee Sweeney, site PI M. Spencer
Title: Failed Regeneration in the Muscular Dystrophies: Inflammation, Fibrosis and Fat
Major Goals: Examination of the immune response in the context of anti-fibrotic therapies.

OTHER SUPPORT

NELSON, STANLEY F.

PREVIOUSLY ACTIVE GRANT HAS CLOSED

PPMD (PI:Nelson) 2/01/2013-01/31/2014 0.3 CM
Title: Pilot Project to Identify Genetic Modifiers of
Duchenne Muscular Dystrophy
To identify novel genetic modifiers of disease progression using a search through the entire human genome for naturally occurring common and rare protein coding variants that modify the progression of muscular dystrophy in humans with DMD location mutations predicted to cause complete loss of function.

PPMD (Nelson) 01/01/2011-12/31/2015 0.6 CM
Title: RNA_SEQ Analysis for Modifiers of Fibrosis
This project is funded by PPMD and is integrated into the UPENN/UChicago/UCLA/UF Wellstone Center to perform RNA_SEQ experiments to assess modulators of fibrosis in mice.

TRX-05426 (PI: Nelson, Co-PI: Miceli) 3/1/2013- 2/28/2015 3.6 CM
California Institute for Regenerative Medicine (CIRM)
Title: Combination Therapy to Enhance AntiSense Mediated Exon Skipping for Duchene Muscular Dystrophy
To perform all preclinical assessment, dose ranging and efficacy and toxicology studies required to enable IND application and 100% clinical trial readiness for a combined therapeutic CDMD51Plus for use in exon skipping for DMD.

1R01NS073871-01A1 (Nelson) 09/01/2011-08/31/2017 2.4 CM
NIH/NINDS $488,500/y
Title: Rapid Phenotyping for Rare Variant Discovery in Autism
This project is intended to use web-based recruiting to greatly expand DNA samples available for genetic analysis to determine the heterogeneous genetic causes of autism.

ACTIVE

P30 AR057230-01 (Spencer) 04/01/2014-03/31/2019 1.2 CM
NIH/National Institute of Arthritis and Musculoskeletal
and Skin Diseases (NIAMS)
UCLA Muscular Dystrophy Core Center
Center will provide support for muscular dystrophy research center.

NIH 1U01HG007703-01 (MPI) 4/01/14-3/31/18 1.2 CM
(E. Vilain, C. Palmer, K. Dipple, S Nelson MPI)
Title: UCLA Undiagnosed Diseases Network Clinical Site
PI will administer and direct clinical assessment and genetic mutation analysis of subjects with rare diseases.

PPMD (S. Nelson, PI) 02/01/17-01/31/21 1.2CM
Title: Whole Genome Sequencing of ImagingDMD subjects
This project is funded by PPMD and is integrated into the UPENN/UChicago/UCLA/UF Wellstone Center to perform whole genome sequencing and interpretation of 120 cell lines from DMD patients to identify genetic modifiers related to fibrosis.

Sponsor Name: University of Florida (S. Nelson PI of NIH Subcontract)
08/01/15-07/31/20 0.6CM

Title: “IMAGING OF FAILED REGENERATION IN MUSCLES OF MUSCULAR DYSTROPHY PATIENTS”
To performe whole genome sequence and RNA analysis of patient derived fibroblasts with DMD mutations.

PPMD (S. Nelson PI) 01/01/17-12/31/17 0.6CM
Title: CDCC Liaison Grant
This project supports clinical nurse coordinator within the CDMD Clinic

PENDING

None